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BY
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PhD Dissertation

by

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PREFACE

This thesis is submitted as a series of papers relying on the three peer-reviewed studies included in the appendix. The thesis covers the background, results and critically reviews the methodology of these studies. Furthermore, the thesis discusses the clinical interpretation and limitations of the studies along with providing perspectives for future research.

Paper 1: Qvist AH, Væsel MT, Jensen CM, Jensen SL. **Plate fixation compared with nonoperative treatment of displaced midshaft clavicular fractures: a randomized clinical trial.** Bone Joint J. 2018 Oct;100-B(10):1385-1391. doi: 10.1302/0301-620X.100B10.BJJ-2017-1137.R3. PMID: 30295536.

Paper 2: Qvist AH, Vaesel MT, Moss C, Jakobsen T, Jensen SL. **No need to use both Disabilities of the Arm, Shoulder and Hand and Constant-Murley score in studies of midshaft clavicular fractures.** Acta Orthop. 2020 Sep 15:1-5. doi: 10.1080/17453674.2020.1820274. Epub ahead of print. PMID: 32928045.

Paper 3: Qvist AH, Væsel MT, Jensen CM, Jakobsen T, Jensen SL. **Minimal Pain Decrease Between 2 and 4 Weeks after Nonoperative Management of a Displaced Midshaft Clavicle Fracture Is Associated with a High Risk of Symptomatic Nonunion.** Clin Orthop Relat Res. 2020 Jul 14. doi: 10.1097/CORR.0000000000001411. Epub ahead of print. PMID: 32675585.

ENGLISH SUMMARY

The overall aim of this thesis was to improve functional results after treatment of midshaft clavicular fractures and to reduce the rate of secondary surgery.

Study I was a randomized clinical trial comparing operative and non-operative treatment of adult patients with displaced midshaft clavicular fractures. 150 patients were divided into two equal groups and followed for one year. We measured the functional outcome as well as recorded the incidence of complications and nonunion. The functional outcome was measured with a patient reported score (Disabilities of the Arm, Shoulder and Hand, DASH) as well as a part patient reported and part examiner reported score (Constant Score, CS). We found that operative treatment reduces the risk of nonunion, but there is no benefit the functional outcome scores compared to nonoperative treatment. Furthermore, there is a risk of complications associated with the operative treatment.

Study II was an analysis of the DASH and CS scores from Study I. The measurement properties of both measuring instruments were analysed and compared. We found that the instruments had similar properties and future studies could rely on the use of the DASH questionnaire alone.

Study III was an analysis of the non-operatively treated patients from Study I. We investigated risk factors for the development of nonunion. We found that minimal improvement in pain scores in the period week two to week four after fracture was associated with a high risk of nonunion.

The findings in this PhD dissertation contribute to the understanding of the treatment of mid-shaft clavicular fractures in adults. Study I contributes to a growing body of evidence suggesting that the only benefit of operative treatment is the reduced risk of nonunion. Study II provides an opportunity to ease the administrative and financial burden in future studies, as it is sufficient to use only DASH as a measuring instrument for functional outcome. Study III identifying slowly decreasing pain as a risk factor for nonunion. This finding must be validated in a new study before clinical use, but has the potential to change the current treatment of clavicular fractures to a more individual approach, where only patients at high risk of nonunion are offered surgery.

DANSK RESUME

Det primære formål med denne afhandling var at forbedre de funktionelle resultater efter behandling af midtskafts brud på kravebenet, samt reducere raten af sekundær kirurgi.

Studie I var et randomiseret klinisk studie hvor man sammenlignede operativ og ikke-operativ behandling af voksne patienter med forskudte midtskafts kravebensbrud. 150 patienter blev fordelt i to lige store grupper ved lodtrækning og blev fulgt i et år. Vi målte det funktionelle resultat samt registrerede forekomsten af komplikationer og pseudoartrose.

Det funktionelle resultat blev målt med en patient raporteret score (Disabilities of the Arm, Shoulder and Hand, DASH) samt en score bestående af både en patient raporteret del samt en del målt af en undersøger (Constant Score, CS).

Vi fandt, at operativ behandling nedsætter risikoen for pseudoartrose, men der ses ingen gevinst i det funktionelle resultat. Ydermere er der risiko for komplikationer i forbindelse med den operative behandling.

Studie II var en analyse af DASH og CS skemaerne fra studie 1. De målemæssige egenskaber ved begge måleinstrumenter blev analyseret og sammenlignet. Vi fandt, at instrumenterne havde de samme egenskaber, og at man i fremtiden kan nøjes med kun at bruge den patient rapporterede score (DASH).

Studie III var en analyse af de ikke-operativt behandlede patienter fra studie I. Vi undersøgte risikofaktorer for udviklingen af pseudoartrose. Vi fandt at langsomt aftagende smerter i perioden uge to til uge fire efter kravebensbrud var associeret med en stor risiko for pseudoartrose.

Fundene i denne Ph.D. afhandling bidrager til forståelsen af behandlingen af midtskafts kravebensbrud hos voksne. Studie I bidrager til en voksende mængde af evidens, der peger mod, at den eneste gevinst ved operativ behandling er den nedsatte risiko for pseudoartrose. Studie II giver mulighed for at lette den administrative og økonomiske byrde i fremtidige studier, da man kan nøjes med kun at anvende DASH som måleinstrument af funktionelt resultat. Studie III identificerede langsomt aftagende smerter som risikofaktor for pseudoartrose. Fundet skal valideres i et nyt studie før klinisk brug, men har potentiale til at ændre den nuværende behandling af kravebensbrud til et mere individuelt fokus, hvor kun patienter med høj risiko for pseudoartrose tilbydes operation.

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I would like to thank my main supervisor Steen Lund Jensen and co-supervisor Thomas Jakobsen. Steen made sure that not a single comma was left unturned, and Thomas provided the bigger picture, when needed. A perfect combination. Furthermore, Steen believed in me years ago, and gave me the freedom to pursue my own ideas, however crazy they may have seemed.

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Last, but not least, I would like to thank my family; the triple L's (Lise, Lillen og Lillebror) and Frederik. Thank you for patience, encouragement and support.

TABLE OF CONTENTS

1. Introduction

Displaced and comminuted midshaft clavicular fractures are common[1–5]. The treatment of midshaft clavicular fractures has traditionally been non-operative supported by early papers reporting a low incidence of non-union and high patient satisfaction following non-operative treatment[4,6]. These early results were based on studies of both undisplaced and displaced fractures in adults as well as children. In contrast to the studies fra 1960s, in the late 1980s, it became increasingly clear that adult patients with displaced midshaft fractures had a high risk of non-union combined with a high risk of unsatisfactory functional outcome after non-operative treatment[7–9]. The first randomized clinical trial comparing operative and nonoperative treatment was published in 2007[10] and showed that patients treated operatively had a reduced risk of non-union along with a slight improvement in functional outcome scores compared to non-operative treatment. To further investigate operative and nonoperative treatment of midshaft clavicular fractures a Danish randomized clinical trial was initiated in 2010 at Aalborg University Hospital, Viborg Regional Hospital and Randers Regional Hospital. The present PhD thesis is based on results from this trial.

2. Thesis at a glance

	Study I	Study II	Study III
Aim	Compare operative and non-operative management of midshaft clavicular fractures.	Compare measurement properties of the DASH and CS score.	Identify and investigate risk factors for development of non-union.
Method	Randomized controlled trial. 150 patients randomized to operative or non-operative treatment. Outcome scores, complication rates, non-union rates were compared	Study of 146 patients from Study I. The measurement properties of the Disabilities of the Arm, Shoulder and Hand and Constant-Murley scores were analysed and compared	Study of the 64 patients treated non-operatively from Study I. Various risk factors for development of non-union were investigated and analysed.
Conclusion	Operative management reduces the risk of non-union but offers no benefits in functional outcome after six months and one year.	DASH and CS have good convergent validity, and it is not necessary to use both in future studies.	Minimal pain reduction in the first weeks following fracture is associated with a high risk of non-union.

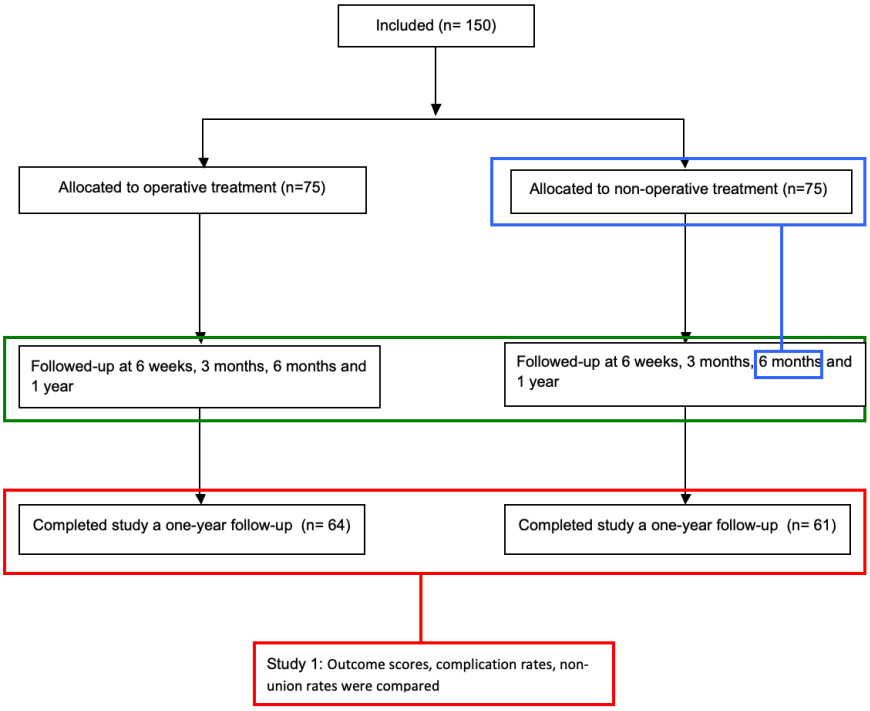


Figure 1. A graphical representation of studies 1-3.
Red box: Study I. Comparison of Outcome scores, complication rates, non-union rates.
Green box: Study II. Measurement properties of DASH and CS compared at each follow-up point.
Blue box: Study III. Risk factors for development of non-union investigated and analysed.
CONSORT flowchart is available in the article for study I[11].

3. Background

3.1 Modern treatment of midshaft clavicular fractures: A summary.

In the 1960s Charles Neer and Carter Rowe independently published two large cohorts of clavicular fractures. These studies are widely regarded as the early foundation for the modern treatment of midshaft clavicular fractures. Following non-operative treatment Neer and Rowe reported low non-union rates of 0.13 and 0.8 per cent, respectively, following non-operative treatment and higher non-union rates of 4.4 and 3.7 per cent, respectively, following operative treatment[4,6].

The perception of operative treatment as a factor in the development of non-union discredited osteosynthesis and the standard treatment of midshaft clavicular fractures continued to be non-operative in the following decades.

In the late 1980s, there was increased focus on patients with displaced fractures, and single cohort studies suggested that this subgroup of patients might have unsatisfactory outcomes[7–9] after non-operative treatment and that operative treatment may yield good results[12].

A metaanalysis performed in 2005[2] on available data of 618 patients with displaced midshaft clavicular fractures showed a significantly lower non-union rate following operative treatment compared to primary non-operative treatment (2.2 % vs. 15.1 %).

In 2006 McKee et al.[13] published a cohort of patients with non-operatively treated displaced fractures and reported that functional outcome as measured by Constant Score[14] (CS) and Disabilities of the Arm, Shoulder and Hand[15] (DASH) score was worse than the published normative value for the general population, indicating room for improvement in the treatment of displaced fractures.

The first randomized trial comparing operative and non-operative treatment of midshaft clavicular fractures was published in 2007 by the Canadian Orthopaedic Trauma Society (COTS)[10]. In this trial, 132 patients with displaced midshaft clavicular fractures were randomized to operative treatment with plate and screws or non-operative treatment with a sling. The rate of non-union was 3.2% following operative treatment and 14.2% following non-operative treatment and at one year follow-up patients in the operative treatment group had a DASH score approximately 10 points better that the non-operative treatment group.

In the following years more randomized trials[16–21] were published and in 2017 a metanalysis[22] on all available randomized studies showed that operative treatment reduced the rate of non-union (1.9 % vs. 16.5 %) and reported a mean DASH score difference of 5.07 points (95% CI 0.06 to 10.08) favouring operative treatment. This difference of 5.07 points is lower than the 10 point clinical relevant difference[23], and it seems that the only long term benefit of operative treatment is the reduction of non-union risk. To reduce the non-union risk from 16.5 % to 1.9 % on a group level would mean that 6.8 patients (The number-needed-to-treat[24] (NNT)) needs operative treatment to avoid one non-union in that group.

The need for a secondary operation was similar in the two groups (17.6 % operative vs. 16.6 % non-operative) with plate removal as the primary secondary operation in the operative treatment group and non-union treatment as the primary reason for secondary surgery in the non-operative treatment group.

The combination of no long term functional outcome improvement and high rate of secondary surgery following operative treatment along with an NNT of 6.8 to avoid one non-union lead the conclusion that the authors "*do not advocate routine plate fixation for all patients, but rather an individualized treatment based on shared decision-making, guided by the presence of risk factors for nonunion and patients' values and preferences.*"

3.2 Complications following treatment of midshaft clavicular fractures

The complications following treatment of midshaft clavicular depends on which primary treatment has been used. Non-union and malunion are the most common reported complications after non-operative treatment. After operative treatment the most common complications is hardware issues and infection.

3.3 Complications associated with non-operative treatment

Definition of non-union

Symptomatic non-union has been shown to be both a painful and debilitating disease[25–27]. Non-union is generally defined as lack of radiological and/or clinical healing along with a specific time limit, but the defining features are ill-defined across the literature. In 1988 the American Food and Drug Administration generelly defined a non-union as "established when a minimum of 9 months has elapsed since injury and the fracture shows no visible progressive signs of healing for 3 months"[28].

In the context of clavicular fractures neither Neer[6], Rowe[4] or Hill[8] defined non-union. In 1998 Robinson[29] defined a time limit of a minimum of 24 weeks from fracture to non-union diagnosis and in 2004 the same author[30] defined union as ”the absence of mobility or pain on stressing the site of the fracture and evidence of bridging callus on radiographs” and nonunion as fractures that did not meet the criteria of union. In a metaanalysis from 2005 Zlowodzki defined non-union as failure of osseous union[2].

In 2014 a systematic review with the aim of identifying predictors associated with non-union and malunion Jørgensen et al[31] found that the time limit defining non-union varied from 16 weeks to 52 weeks, and some reviewed studies did not define non-union at all. In a

metaanalysis of randomized trials Woltz found similar variations in defining time limit along with the use of either computer tomography (2 studies) or radiographs (4 studies) to establish the absence of cortical bridging[22].

Non-union rates

Following the series reported by Neer[6] and Rowe[4], the rate of non-union after non-operative treatment of clavicular fractures was believed to be lower than one per cent. In these studies both adolescent and adult patients were included, displaced and undisplaced fractures were pooled together and operative treatment was performed on some of the displaced fractures; all factors which may have lead to underestimation of the true rate of non-union in adults. In 1997 Hill showed a 15 per cent rate of non-union in a cohort of non-operatively treated displaced midshaft clavicular fractures, which suggested that the risk of non-union in this subpopulation could be substantially higher than previously believed[8]. Similar to the findings of Hill[8], Robinson showed in 1998 that 9.4 per cent of cases with complex comminuted displaced midshaft fractures went on to develop a non-union[29]. Based on non-randomized studies a metaanalysis[2] from 2005 showed a 15.1 per cent non-union rate and in 2017 a metaanalysis[22] based on randomized studies showed a 16.5 per cent non-union rate, and given these rates, non-union appears to be much more common than previously believed.

Due to the high rate of non-union and the associated disability of symptomatic non-union; non-union is the single most common and one of the most disabling complications following non-operative treatment.

Malunion

The increased awareness of potential malunion following nonoperative treatment of midtshaft calvicular fractures has been attributed to Eskola[7] and Hill[8], but earlier reports of malunion following midshaft clavicular fractures can be traced back to a case series from 1980 describing subclavian-axillary vein compression of musculoskeletal origin[32]. In the mid 1990s malunion seems to be purely defined as a fracture healed with deformity, as Simpson[25] describes that "*most patients with malunion function well*". In 1998 Nordqvist[9] defined malunion based on radiographic findings, stating that malunion was present, if the fracture had united "*with more than one bone width of fragment displacement or angulation of >30 degrees".* This radiographic definition is not adopted across the literature, and in 2003 McKee[33] states that *"Radiographic evidence of malunion is universal following displaced fractures of the clavicle*", meaning that all displaced fractures heals with a deformity.

Brachial plexus compression and thoracic outlet syndrom[34] along with more broad symptoms such as dysfunction and pain[13,33] has been attributed to malunion.

In the recent randomized studies malunion was defined as the combination of radiographic union with deformity and the presence of broad clinical undefined symptoms such a weakness, fatigue or neurovascular deficiets[10,16]. One study diagnosed malunion if surgery for symptoms thought to be related to deformity had been perfomed[20]. In other studies malunion has been reported without a definition[18], mentioned but not reported[21] or not defined or reported at all[17,19]. No studies gave a defining time frame for the diagnosis of malunion.

For midshaft clavicular fratures various degrees of shortening has been associated with malunion, however a large systematic review did not find no significant association between fracture shortening and shoulder outcome scores[35].

3.4 Complications associated with operative treatment

The most common complications after operative treatment are implant related, where the revision rates vary from 9% to 64% following operative treatment[36]. In a metaanalysis of randomized controlled trials Woltz reports a secondary surgery rate of 17.6%[22], whereof most surgeries are implant removals, mostly due to hardware irritation. Hardware failure and secondary dislocation are not common.
In general, infection rates are lower than 10%, and most infections are superficial[22,36]. Brachial plexus symptoms and regional pain syndromes can be common with a reported rate up to at 38%, but are for the most part transient[22,36]. Persistent numbness of the skin is common with a reported range of just below 20%[18,20]. In randomized studies, the rate of non-union following plate fixation is lower than 2%[21,22].

3.5 Functional outcome scores used in clavicular fracture research.

With the purpose of evaluating outcome after nonoperative treatment of midshaft clavicular fractures with patient-oriented health measures and objective muscle-strength testing McKee used both the CS and DASH score in 2006[13]. The use of both CS and DASH in the evaluating of midshaft clavicular fractures was widely adopted and used in most of the subsequent randomized controlled trials[21,22].
In 1987 CS was developed as a clinical method of shoulder function assessment[14]. DASH was developed in 1996 with a of purpose of assessing symptoms and functional status in populations with upper extremity musculoskeletal conditions[15].
The CS score ranges from 0 to 100 points with 100 point representing a healthy functioning shoulder. The examiner reported part (range of motion and power) of CS accounts for a total of 35 points, while the patient reported part (pain and activities of daily life) accounts for a

total of 65 point, with one question regarding pain accounting for 15 points.
The DASH score ranges from 0-100 points based on a 30 item self-reported questionnaire. A DASH score of 0 points represents normal shoulder function.
The use of CS introduces observer bias and the measurement of power poses a problem, as some healthy individuals lack the ability to score the maximum 25 points on the power subscale[37–39].
Good convergent validity may exist between DASH and CS, as good correlation between the scores has been shown in different shoulder pathologies including clavicular fractures[40–43].

3.6 The Development of Patient Related Outcome Measurements

Three stages exist for the development of patient related outcome measurements (PROM)[44,45]. The first stage is generation of questionnaire items thru a review of the background literature. All relevant items are included. The second stage is item reduction. Experts review the proposed items, and the items are tested on patients in a small-scale study. The item list is then reduced. After initial item reduction the item list is tested in large scale on patients and further reduced based on statistical methods and judgment by experts and patients. Finally, at the third stage, the reliability, validity, responsiveness and interpretability of the PROM is assessed[46,47].
Overall the reliability of a PROM relies on the PROMs ability to measure the same scores in different settings of repeated measurements. The repeated measurements could be: over time (test-rest of patient with unchanged health status), by the same person on different occasions (intrarater), or using different sets of items from the same PROM (internal consistency). The validity of a PROM is an evaluation of the degree to which the instrument measures the constructs it is developed to measure; does the PROM relate to a gold

standard and does different scores relate to other similar measures as expected based of previously hypotheses concerning this relationship? Responsiveness is a measure for the PROMs ability to detect a change in health status of time. Interpretability is the ability to assign qualitative meaning to the PROM scores and changes in scores.
In the development of the DASH questionnaire the first stage of item generation led to the identification of 821 items of interest[15]. A group of three experts reduced the list to 177 items, which was further reduced to 78 items, after further review and small scale pretesting on patients. The 78-item questionnaire was then tested in large scale on patients and reduced to the known 30-item DASH questionnaire[48]. A reliability, validity, responsiveness study was then performed, and the questionnaire was found to have sufficient validity and responsiveness in both proximal and distal disorders of the upper extremity[49].

3.7 Risk factors for the development of non-union

In an attempt to identify patients at high risk of non-union following non-operative treatment various risk factors for the development of non-union has been described.
In 1997 Hill[8] reported that fracture shortening ≥ 2 centimetres was associated with the development of non-union. In this retrospective study of 52 midshaft clavicular fractures no association between age, gender, occupation, smoking status, mechanism of injury, or the presence of associated injuries and non-union was found.
In another retrospective study of 185 fractures with a average follow-up of 17 years, Nordqvist[9] found no evidence that the risk of non-union could be based on the appearance of the fracture. In a case series of patients referred with persistent symptoms after non-operative treatment of midshaft clavicular fractures Wick found that 91%(n=30) of the fractures were shortened by at least 2 cm, and recommended that these fractures should be treated with osteosynthesis, if there were no callus formation after 6 weeks. Kirmani[50] found no difference in secondary surgery (due to

symptomatic non-union) rates between a cohort with the radiological signs of a intermediate vertical fragment and a cohort with no sign of such fragment.

Postacchini[51] reported a case series of nonoperatively treated midshaft fractures with mean follow-up of 8.7 years and found that the presence of a third fragment did not predispose to failure of fracture healing. The study reported that patients with non-union had less radiographic displacement and more shortening compared to patients with union, but of this difference no statistical analysis or confidence intervals were reported.

In a systematic review of these retrospective cohort and case series studies with the aim of identifing predictors associated with nonunion or symptomatic malunion Jørgensen[31] found that displacement was most likely a predictor for non-union, while evidence for other factors (smoking, fracture comminution, age , gender and shortening) was limited.

Most of the recent randomized controlled trials did not explore for potential association between baseline characteristics and non-union[16,19–21]. The Canadian study[10] found an association between total displacement (combined vertical displacement and shortening at the fracture site) and inferior DASH scores at one year in the nonoperative group. As non-unions in this study were untreated and included in the one-year end analysis, inferior DASH scores at that time point could be due to negatively influence from the non-union cases. Association between non-union and increasing displacement was found by Virtanen[17]. In a combined analysis of operatively and non-operatively treated patients Robinson[18] showed that positive smoking status was associated with non-union.

Three prediction models for estimating the risk of non-union have been developed:

1: In a prospective cohort from 2004 based on 581 midshaft fractures with the aim of estimating the risk of non-union following non-operative treatment Robinson[30] found that risk of non-union increased

with the presence of displacement and comminution along with increasing age and female gender. Robinson used Cox Regression Modelling to calculate a diagnostic index, where the above-mentioned factors were given different weights, and the diagnostic index could be used to estimate the risk of non-union at six, twelve, and twenty-four weeks.

2: A more simple approach was taken by Murray[52] in 2013, where the risk of non-union in 941 displaced fractures was examined. Murray found that the presence of comminution and positive smoking status increased the risk of non-union. Non-union risk increased with increasing fracture displacement. A Logistic Regression Model was developed to estimate the risk of non-union. This model showed more than 90 per cent risk of non-union in a patient with positive smoking status and a comminuted fracture with 4 centimetres of displacement.

3: In a new study with a cohort of 200 patients it was found that at six weeks a QuickDASH score of ≥40 points, no callus on radiographs, and fracture movement on examination were significant predictors of nonunion[53].

Other studies have shown that pain and early poor clinical results may be possible predictors for non-union. Pain at rest at 4 weeks follow-up was found to be more present in patients with non-union compared to patients with union in a 2004 study examining 222 fractures[54]. In the same cohort Nowak[55] also reported that displacement and comminution was associated with patient reported fracture sequelae after 9 to 10 years of follow-up. In a study based on data from a previous randomized trial[30] Clement[56] showed that both smoking and a DASH score of > 35 points at six weeks following fracture was associated with the development of non-union.
Most recently a study[57] showed that the sonographic absence of bridging callus at six weeks was associated with non-union. In this study positive smoking status was also found to be associated with

non-union while age, comminution and gender was not. The clinical usefulness of these models remains unclear, as none of the mentioned prediction models have been externally validated. The variables used in prediction modelling can be classified as "Patient Specific", "Fracture Specific" or as proxy variables for healing (Fig 2).

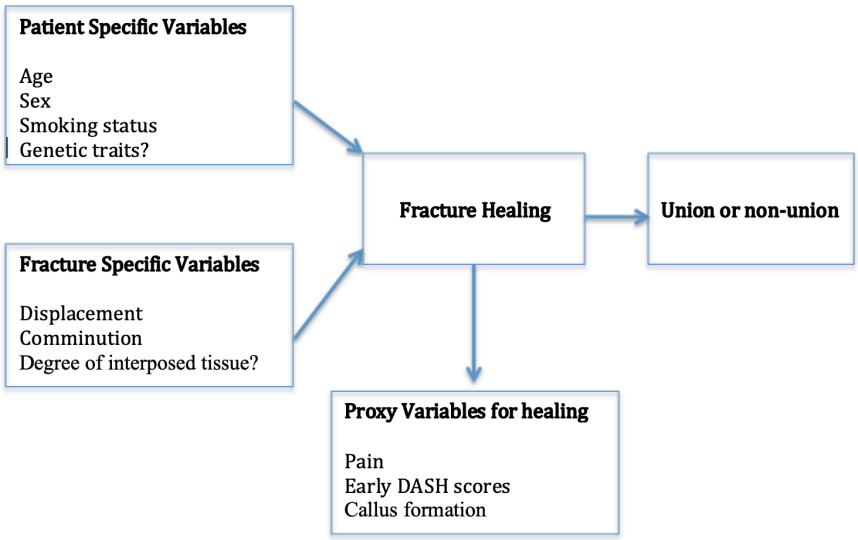


Fig 2. A model for prediction of fracture healing. The variables listed are examples of possible predictors.

Both the patient specific and fracture specific variable group has the potential to contain undiscovered or unstudied variables such as "Generic predisposition to slow healing" or "Degree of interposed tissue". This problem of unknown predictor variables could be bypassed by using proxy variables for healing[58]. A proxy variable for healing is an indirect measurement of fracture healing, and contains all the effect of all possible known and unknown patient specific or fracture specific variables. This means that a good proxy variable could predict non-union risk without information about the baseline characteristics of the patient specific or fracture specific variables.

4. Aim and hypotheses

The overall aim of this thesis was to improve functional results after treatment of displaced midshaft clavicular fractures and to reduce the rate of secondary surgery.

Study I.

Null hypothesis: Operative treatment with locking plate and screws yields no changes in functional outcome scores and no reduction in nonunion rates compared to non-operative treatment in displaced midshaft clavicular fractures.

Alternative hypothesis: Operative treatment with locking plate and screw yields improved functional outcome scores and a reduction in nonunion rates compared to non-operative treatment in displaced midshaft clavicular fractures.

Study II.

Null hypothesis: There is no convergent validity between Disabilities of the Arm, Shoulder and Hand and Constant-Murley scores in patients with displaced midshaft clavicular fractures.

Alternative hypothesis: Convergent validity exists between Disabilities of the Arm, Shoulder and Hand and Constant-Murley scores in patients with displaced midshaft clavicular fractures.

Study III.

Null hypothesis: Minimal Pain Decrease in the early weeks following fracture is not a risk factor for development of non-union following non-operative treatment of displaced midshaft clavicular fractures.

Alternative hypothesis: Minimal Pain Decrease in the early weeks following fracture is a risk factor for development of non-union following non-operative treatment of displaced midshaft clavicular fractures.

5. Methodological considerations

5.1 Ethical Considerations and permissions

Data for all studies was obtained through a single randomized controlled trial. Overall design is presented I fig. 1. The study was approved by the Scientific Ethics Committee of the Region of Northern Jutland (N-20090054) and the Danish Data Protection Agency (j.nr. 2013-41-1457). All patients gave their informed content to participate. The project was registered with www.clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01078480). The study was performed in accordance with the ethical principles of the Helsinki Declaration.

5.2 Overall design considerations

Study population

The study population was defined by inclusion and exclusion criteria as available in table 1

Inclusion criteria
1. Age between 18 and 60 years 2. Displaced midclavicular fracture
Exclusion criteria
1. Bilateral fractures 2. Impending perforation of the skin 3. Open fracture 4. Neurovascular injury 5. Another fracture in the same limb 6. Pathological fracture 7. A history of symptoms from the shoulder 8. Previous clavicular fracture 9. More than two weeks since the injury 10. Cognitive impairment 11. Inability to follow the protocol of treatment 12. Contraindications to general anaesthesia or surgery

Table 1. *Inclusion and Exclusion criteria for study 1.*

The age limit for inclusion primarily had the purpose of excluding children and adolescents in which the healing rates are different and plate osteosynthesis is not considered a first choice. The age limit was set at 60 years to exclude older patients, where the risk of failure and complications could be high compared to a younger population.

Furthermore as we expected the mean age for the population to be lower than 40, the inclusion of a few older patients with a high risk of complications could skew the results in either group. Also, a population older than 60 could meet a wide range of the exclusion criteria, which would limit the generalizability of the study, if a large group of screened patient was excluded.
The exclusion criteria excluded patients with traditional indications for surgery such as impending perforation of the skin, open fracture, neurovascular injury and to a lesser extent pathological fracture and another fracture in the same limb. Conditions such as bilateral fractures, a history of symptoms from the shoulder or previous clavicular fracture could potentially affect DASH and Constant scores, and were also excluded.

Intention to treat principle

In study I patients were followed based on initial randomization according to the intention-to-treat principle[59,60]. This means that patients with surgical treated non-union after nonoperative treatment were analysed together with the remaining nonoperative treatment group. Similary a patient in the operative treatment group who declined surgery was followed in the operative treatment group. Intention-to-treat analysis is used to minimize bias in randomized controlled trials and deals especially with issues of noncompliance and missing data[60]. Reflecting a true clinical setting the intention-to-treat principle is used to compare treatment strategies where patients may not always adhere to a strict treatment protocol. With increasing deviations from the treatment protocol, an intention-to-treat analysis gives more information about difference between the treatment strategies than the absolute difference between treatments. The intention-to-treat principle *"is generally interpreted as including all patients, regardless of whether they actually satisfied the entry*

criteria, the treatment actually received, and subsequent withdrawal or deviation from the protocol"[61], which was not done in our study, as patients lost to follow-up were not included in end analysis. A true application of the intention to treat principle can only occur if complete outcome data are available for all randomized subjects[60]. No consensus exists about the treatment of incomplete data and numerous methods for imputation of missing data exist[61]. In study I, II and III patients lost to follow-up were excluded from end analysis and outcomes were not imputed, and the use of the intention-to-treat principle in this study is more an overall design feature with the intent of analysing non-unions in the nonoperative treatment group and comparing treatment strategies, than the application of a specific statistical analysis method.

Midclavicular and Displacement definition

In this study "midclavicular" was defined as the middle one third of the clavicula. In other randomized studies the definition of "midshaft" varies from the "intermediate three-fifths of the diaphysis"[18,20,21] to the "middle-third"[17,19] to no definition at all[10,16]. In this study a displaced fracture was defined as a fracture with no cortical contact between the two main fragments on at least one of two radiographs. This definition was adopted from the COTS randomized trial[10], as no clear definition of displacement existed in the literature. In later randomized trials the definition of displacement varies from "at least 1 shaft width"[17,18,20,21] , "no cortical contact"[19] or no definition is given[16].

Radiographs

As standard two radiographs was taken with an anteroposterior direction and a 30° angle between the projections in the sagittal plane.

No control of radiologic technique was planned, and it is possible that projection technique varied between centres. None of the other randomized trails specify theirs radiographic technique. All radiographs were reviewed at study completion.

Follow-up

Clinical and radiographic follow-up occurred after six weeks and after three, six, and 12 months. The timeframe and intervals for follow-up and one-year follow-up was considered to be standard at the time. This timeframe and the intervals for follow-up are in general similar in all following randomized trials.

5.2 Outcomes

The Disabilities of the Arm, Shoulder and Hand questionnaire

The primary outcome in study I was the score of Danish version of the disabilities of the arm, shoulder and hand (DASH) questionnaire[15] at one-year follow-up. The DASH questionnaire was developed with a systematic approach and a defined purpose of assessing symptoms and functional status in populations with upper extremity musculoskeletal conditions[15]. The DASH score is a 30 item self-reported questionnaire, with most questions covering activities of daily life and symptom severity. Questions are answered by response of: ”No difficulty”, ”Mild difficulty”, ”Moderate difficulty”, ”Severe difficulty”, ”Unable” or a similar range. Points on a range from 1-5 are assigned to each response. The DASH score is calculated as the average of assigned values for all completed responses, which produces a score from 1 to 5. This value is transformed to a score out from 0 to 100 by subtracting one and multiplying by 25. A DASH

score cannot be calculated if 4 items or more are missing. A DASH score of 0 points represents normal shoulder function and a score of 100 represents severe disability. A 10 point difference between in mean DASH score is considered to be the minimal important change[23]. The Danish version of DASH questionnaire was validated in patients with fractured wrists in 2011[62]. Overall the DASH questionnaire has been widely validated[63], but is not validated specificly in patients with clavicular fractures. The DASH questionnaire should be considered as a score for general upper extremiy function and not shoulder specific.

Constant score

The Constant Score[14](CS) is a shoulder specific score that ranges from 0 to 100 points with 100 point representing normal shoulder function. CS combines performance-based measures with patient reported outcomes. The performance-based measure is an examiner reported evaluation of range of motion and strength for a total of 65 points. The patient reported outcomes (pain and activities of daily life) accounts for a total of 35 point, with one question regarding pain accounting for 15 points. Due to confusion surrounding the measurement of strength, updated guidelines for the use of constant score was published in 2008[64]. The 2008 guidelines states that strength should be measured with a isometric dynamometer placed at wrist level with the shoulder at 90 degrees of abduction in the scapular plane. If the patient is unable to achieve 90 degrees of abduction, a strength score of zero is assigned. In the present studies strength was measured with a isometric dynamometer (Mecmesin Myometer, Mecmesin, West Sussex, UK) according to the 2008 guidelines. In a study of rotator cuff surgery the minimal clinical relevant difference for the CS has been shown to be 10.4 points[65]. The documentation of the development of CS is lacking, and no systematic approach seems to have been applied in the development of the score, where subjective and objective measurements are arbitrary combined with no reasoning

for the selection of items or weight of each item. Despite the shortcomings in development CS is widely accepted as a measurement for shoulder function[63]. In 2016 Ban et al. found high interrater reliability, high convergent validity and good internal consistency of the total CS for patients with clavicle fractures after aplciation of a new standardized measurement protocol. Overall no golden standard for the functional measurement of the shoulder exists, but after McKees study on deficits following nonoperative treatment of midshaft clavicula fractures[13] both DASH and CS have been adopted as the reference points in midshaft clavicula fracture research.

Pain

Patients reported current pain from the facture site on a visual analogue scale once a week in the first six weeks following fracture.

Fig 3. Picture of VAS scale in pain diary. The scale was 10 cm, with no pain at the left end of the scale and worst imaginable pain at the right end of the scale.

Non-union

Nonunion was defined as radiographic lack of callus formation, persistent fracture lines, and/or sclerotic edges of the bones at the fracture site at six months. The nonunion was regarded as symptomatic if these findings were combined with pain at the fracture site, tenderness and local crepitation. Nonunion was diagnosed and treated independently at each centre.

Complications

Complications such as infection, neurovascular damage or adhesive capsulitis were registered at each follow-up point. At six months patients with symptomatic hardware were offered plate removal, if the fracture was united. Complication registration was done at each centre without a specific definition for each possible complication. No complication reporting classifcation was used.

5.3 Sample size calculation

Risk of type I error (α) was 5% and the power (1-β) was set to 80%.

A standard deviation (σ, SD) of 20 points for the DASH score was assumed and clinically relevant difference (d) in DASH score was 10[23]. DASH score was chosen as the primary outcome based on the COTS randomized trial[10]. SD was arbitrary set to 20, as earlier studies[10,13] did not provide a SD for DASH scores.

Sample size for each group[66] was calculated as:

$n_a = ((Z_a + Z_{1-b})^2 \text{ x } 2 \times \sigma^2)/d^2$

$n_a = ((1.96 + 0.84)^2 \text{ 2 x } 20^2))/10^2$

$n_a = (7.84 \text{ x } 2 \text{ x } 400)/100 = 62.7$

63 patients were required in each group. Allowing for loss to follow-up, the recruitment was increased to 150 patients in total

5.4 Randomization

The randomization table was computer-generated. Allocation was

concealed with sealed envelopes and stratified by the surgical centre using blocks of ten. Each block had an equal allocation of non-operative and operative treatments.

5.5 Blinding

Per design blinding of surgeon or patient was not possible. A specialist nurse blinded to treatment recorded the Constant score and the patients were encouraged not to tell which treatment they had received, and clothes covered both shoulders.

5.6 Data collection

Data was collected locally on paper forms. At the end of the study all data was entered into a central database. Validation was done by double data entry.

5.7 Non-operative treatment

Patients were treated with a sling (Collar'n'Cuff, Mölnlycke Health Care, Sweden) for a maximum of three weeks. Use of arm and shoulder within the limits of pain was allowed. Patients were not offered physiotherapy.

5.8 Operative treatment

Operative treatment was completed within 14 days of the injury. General anaesthesia and a single dose of intravenous prophylactic

antibiotic were used. The fracture was exposed and reduced before stabilizing with precontured plate and locking screws. At least three bicortical screws were placed in each main fragment, and two of those were locking screws. Postoperatively patients were treated with a sling (Collar'n'Cuff, Mölnlycke Health Care, Sweden) for a maximum of three weeks. Use of arm and shoulder within the limits of pain was allowed. Patients were not offered physiotherapy.

5.9 Treatment of non-union and complications

The treatment of symptomatic non-union consisted of surgery with debridement, reaming of the medullary canals, and fixation with a plate. Autologous bone graft was used if necessary.
Other treatment failures were treated according to centre guidelines.

5.10 Bias considerations

Randomized trials are considered to be at the top of the evidence hierarchy, as randomization is an excellent tool to reduce bias. However some potential for bias arises from the randomized controlled trial design. According to the Cochrane handbook for systematic reviews the specific domains for risk of bias in randomized trials are: (1) bias arising from the randomization process,
(2) bias due to deviations from intended interventions, (3) bias due to missing outcome data,
(4) bias in measurement of the outcome, (5) bias in selection of the reported result[67].

(1) bias arising from the randomization process

Bias can occur in the randomization process when patients are accepted or rejected to participate in a trial, or when the intervention is allocated. The bias occurs when the investigator interferes (consciously or unconsciously) with study inclusion or treatment allocation based on knowledge of the randomization. In this study we used blocks of ten patients with an equal treatment allocation. In the present studies there is a risk of bias as allocation concealment is reduced since there is a known number of each treatment allocation in a block. Depending on the sequence the envelopes are opened, one or more of the last allocations may be known.

(2) bias due to deviations from intended interventions

Possible bias due to deviations from intended interventions depends on the trial setup (‘intention-to-treat” or ‘per-protocol”). This study was designed to study the effect of assignment to the intervention at baseline (‘intention-to-treat”), and in that context the possible deviations are those that:

(a) could arise because of the trial context:

The lack of blinding of study participants could lead to a situation, where participants allocated to nonoperative treatment feels “unlucky” and drops out to seek surgical treatment elsewhere. Furthermore investigators, who are not blinded may give increased attention to a certain treatment group and thus introduce bias. A surgeon biased towards surgical treatment might give increased attention to this group as a whole, which would affect the results of the trial. The increased attention could come in the form of clinical visits more frequent than specified in the study protocol or simply more positive attention during planned clinical visits. Clinical visits beyond the specified follow-up time points were not registered in the trial. Furthermore

secondary treatment and investigations after treatment allocation could be based on the knowledge of the treatment allocation. Blinding is difficult in surgical trials, and blinding of study participants or surgeons was not an option in the present study.
A possible overestimation of non-union risk could arise due to delayed inclusion. Patients with decreasing pain might not be willing to participate in a study with a risk of surgical treatment when asked late (14 days) in the study inclusion period. If pain were associated with non-union this would lead to an overestimation of non-union risk as patients with low risk would not be willing to participate in the study.

(b) would be inconsistent with the trial protocol:

Inconsistency with trial protocol could range from simple deviations such as changes in follow-up or the use of a different type of sling to the more severe case such as the use of non-protocolized surgical techniques. As all radiographs were reviewed at study completion any major deviations from the trial protocol would be detected at this time point.

(c) could influence the outcome:

This study was designed to study the effect of assignment to the intervention at baseline. If a large number of patients did not receive the intended intervention, several possibilities for over- or underestimating treatment effects would arise. An example of this could be a scenario where patients in the non-operative group opt for surgical treatment due to pain issues in the early weeks following fracture. This could lead to an underestimation of non-union risk in the non-operative group, as surgical treatment reduces the risk of non-union. In this effect a per-protocol analysis would also be of little

value, as the allocation to either treatment would no longer be randomized.

(3) bias due to missing outcome data

This type of bias could occur, when there are systematic differences between the two groups withdrawing from the study. It could be present in this study if patients in the non-operative group withdraws to seek surgery elsewhere, and if patients withdraws because their outcome is good and they no longer feel the need to be reviewed.

(4) bias in measurement of the outcome

This type of bias could occur when a systematic difference in the observation of treatment results is present. Study participant or investigators may affect outcome measurements based on the knowledge of the treatment allocation. In the present study we sought to reduce the risk of detection bias by encouraging the participants not to tell which treatment they had received, and by covering both shoulders with clothes as to blind the specialist nurse who recorded the Constant Score. As the participants were not blinding the DASH scores and the patient reported parts of the Constant Score could be potentially be influenced by bias.

(5) bias in selection of the reported result.

This type of bias occurs in situations where outcome measures (end-points) or statistical analysis are specified post hoc based on available data; when only the most favourable result from a variety of different measurements is reported or when reporting the most favourable result of multiple possible adjustment in the statistical analysis. This type of bias is often seeked to be reduced by publishing study

protocols and statistical analysis plans prior to study completion. At the time of planning this study, the publishing of study protocols and statistical analysis plans was not considered as standard procedure.

5.11 Special methodical considerations.

The following describes special considerations for each study. A full presentation of methods is available in the respective studies.

Study I considerations

By presenting the option of plate removal to patients with symptomatic hardware there is a risk of inducing plate removal. The same kind of risk is present in the treatment of non-unions, where patients are closely followed and offered treatment at six months if a symptomatic non-union is present. The option of plate removal and the close following of possible non-unions both introduces a risk of overestimating the rate of secondary surgery compared to normal clinical practice. In both cases normal clinical practice is that patients with sequelae from either operative or non-operative treatment is referred by their general practitioner to an orthopaedic specialist, which does not fit the trial setup in study I.

Study II considerations

Study II examines the convergent validity between DASH and Constant score based on the assumption that both scores tests for disability following midshaft clavicular fracture. As patients in the

cohort are otherwise healthy in regard to shoulder function, this assumption is believed to be valid. No golden standard to assess disability following midshaft clavicular fracture exists, and therefore only a comparison between DASH and Constant score is possible.
In study II the Bland-Altman plot is used to study the agreement between the two scores. The width of the confidence intervals surrounding the estimates is determined in part by the sample size. Martin Bland[68] recommends a sample size of 100.
In correlation, power calculations are used when determining whether a correlation coefficient differs from zero. If the expected correlation coefficient is low, a large sample size is required than if a higher correlation coefficient is expected[69]. We expected moderate to high ($r > 0.5$) correlation between the two scores, which requires a minimum sample size of 29 patients.
The minimum sample size for both analyses is achieved in study II, where the sample size is 146 for the Bland-Altman plot and 123 for the correlation calculations.

Study III considerations - Pain

Study III examines pain as a risk factor for the development of non-union. In the study current pain from the fracture site is reported on a visual analogue scale (VAS). The reporting of pain on a visual analogue scale has been widely studied and used since the 1970s, and is considered to have good reliability and construct validity[70–75]. Study III does not further explore a single absolute pain score at week four as a possible predictor. This is due to the fact that a range of different characteristic such as age, race, gender and socioeconomic status[76–79] influence pain perception. Some of this influence disappears when pain changes over time are examined[80]. As pain reported on the visual analogue scale have ratio properties[81–86] we believe that VAS_{ratio} has the potential to exhibit good clinical reliability. The

minimal clinical important difference in patients with acute pain was in a large systematic review found to be between 8 – 40 mm on a 100 mm scale[87]. The authors find that patients with higher pain require greater decrease to perceive relief, and conclude that relative changes in pain is a more stable indicator of clinically important difference. This further supports the use of the ratio properties of VAS in our study.

Study III considerations - Prediction modelling

Unfortunatly the small sample size in study does not allow for the development of a predictor model. Prediction models should be internal and external validated[88–92] before widespread clinical use. In general interval validation is used as a tool to evaluate and correct the overfitting/optimism of the model, and external validation is a tool to assess the generalizability of the predictor model[88–92]. For internal validation with an event rate of 17.2 per cent a sample size of 219 patients would be required[93], and as a rule of thumb a mimium of 100 events[94] is required for external validation. Thus our dataset of 64 subjects only allows for an examination of the possible association between pain and non-union risk.

5.12 Study Statistics

All statistical analysis was conducted using Stata (versions 13.1 - 15.0, Stata Corp, College Station, Texas) and R[95]. Data was examined for normality with histograms and QQ-plots and Shapiro-Wilk test. Patient demographics were reported using descriptive statistics. Continuous variables were analyzed using Student's t-test for normally distributed data and Mann–Whitney U test for non-Gaussian distributed data. Categorical variables were tested using chi-squared test or Fisher's exact test if one value was five or less. In study II an inverted DASH (iDASH equal to 100 minus DASH) score was used.

The level of significance was set at $p < 0.05$. A full presentation of statistical methods is available in the respective studies.

6. Main Results

6.1 Study flow diagram

167 patients were assessed for eligibility and 150 patients were enrolled and randomized 1:1 to either operative or non-operative treatment. At study completion 60 patients in the non-operative group and 64 patients in the operative group were available for analysis (Fig. 4). Patient demographics are available in table 2.

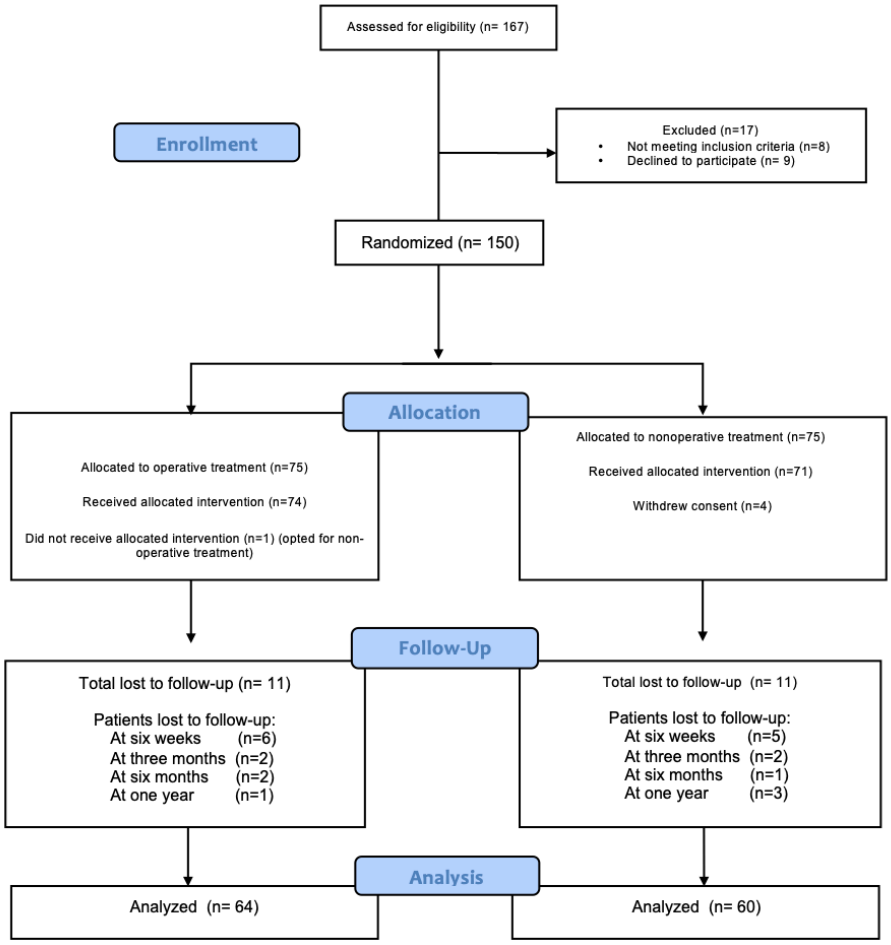


Fig. 4. Study 1 CONSORT flow chart. Unedited, pre-publication version reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery[11].

Table I Demographic Data and Fracture Morphology		
Parameter	Nonoperative treatment (n=71)	Operative treatment (n=75)
Age (yr)	39 (18-60)	40 (18-60)
Age 18-30: 31-45: 46-60 yrs (n)	19:30:22	19:29:27
Male:female ratio (n)	55:16	64:11
Smoker:Non-smoker (n)	16:53	18:54
Shoulder straining work (%)	51	42
Fracture at dominate arm (yes:no, n)	29:39	30:44
Non-comminuted:comminuted fracture (n)	20:48	26:46
Shortning <1:1-2:>2 cm (n)	20:32:16	18:32:21

Table 2. Patient demographics and fracture morphology. Unedited, pre-publication version reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery[11].

6.2 Study I

Funtional Outcome

DASH and Constant score were of normal distribution only at 6 weeks follow-up. Due to ceiling effect data was heavily skewed at subsequent follow-up and Mann–Whitney U test was used for all analysis of DASH and Constant score. Both DASH (Fig. 5) and Constant score were significantly better in the operated group at six weeks and three months ($p < 0.001$ at six weeks and $p = 0.02$ at three months for both scores). At six months and 12 months follow-up there were no difference between the two groups (Fig. 5).

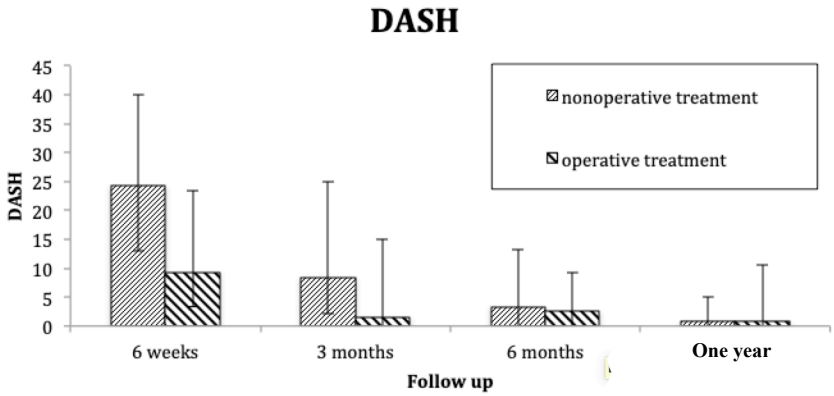


Fig 5. Bar chart showing median Disabilities of the Arm, Shoulder and Hand (DASH) scores during follow-up. Error bars indicate interquartile range. Unedited, pre-publication version reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery[11].

Union Rates

Eleven patients out of 63 patients (17%, 95% CI 9.1 to 29.1) in the non-operative treatment group developed a non-union. In the

operative treatment group, 2 patients out of 65 patients (3%, 95% CI 0.0 to 7.1) developed non-union, which was significantly fewer than in the non-operative group (p = 0.009) (Table XXX). 11 of the non-unions in the non-operative treatment group were symptomatic and nine patients underwent a secondary surgical procedure for non-union. In the operative treatment group, the first non-union case was treated with only two screws in each main fragment instead of three as per protocol. The second non-union occurred in a patient, who declined surgery after randomization to the operative treatment group. The patient was followed in the operative group according to the intention-to-treat principle[59]. The number-needed-to-treat (NNT) operatively in order to avoid one nonunion was seven.

Treatment	Union (n)	Non-union (n)
Non-operative	52	11
Operative	63	2

Table 3. Union and non-union cases after non-operative and operative treatment.

Complications.

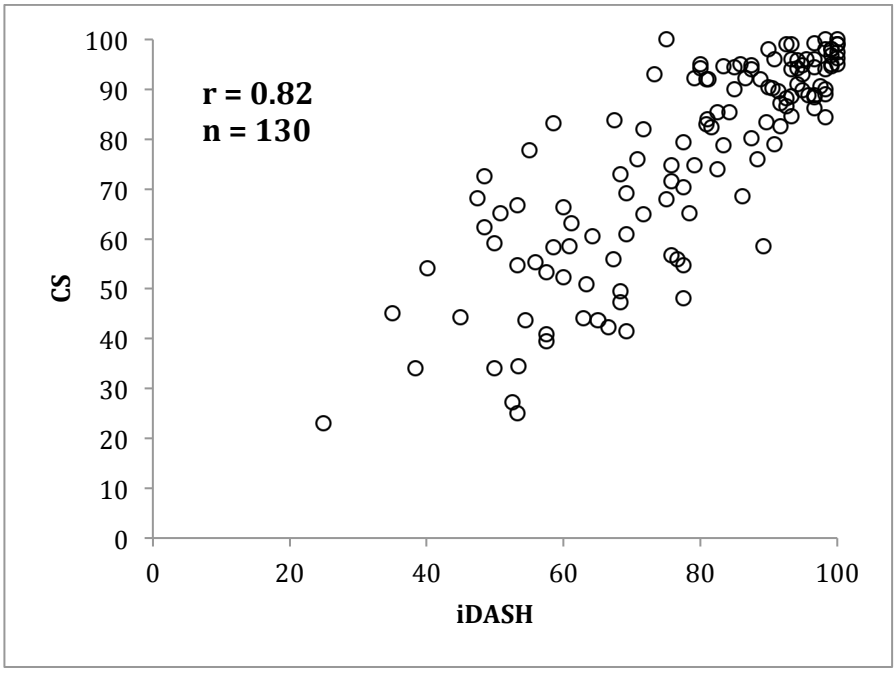
One patient in the operative treatment group was revised due to hardware failure, where perioperative cultures subsequently showed **Cutibacterium**. The major reason for secondary surgery in the operative treatment group was removal of symptomatic metalwork, which occurred in 16 patients (25%, 95% CI 16.0 to 36.8) after six months. One patient sustained a new fracture after plate removal, more medial than the index fracture. This fracture healed after non-operative treatment. After one year, complaints of dysaesthesia around and below the fracture site were present in 13 patients (21%, 95% CI 13.3 to 33.6) in the non-operative group and 44 patients (70%, 95% CI 55.6 to 77.8) in the operative group.

6.3 Study II

In study II, 146 patients were included. 71 patients were from the non-operative treatment group and 75 were from the operative treatment group. Overall, we found similar measument properties between iDASH and CS.

Correlation

The correlation between iDASH and CS decreased increasing follow-up and was found to be high at six weeks, three months and six months follow-up and moderate at one-year follow-up (Fig. 6).



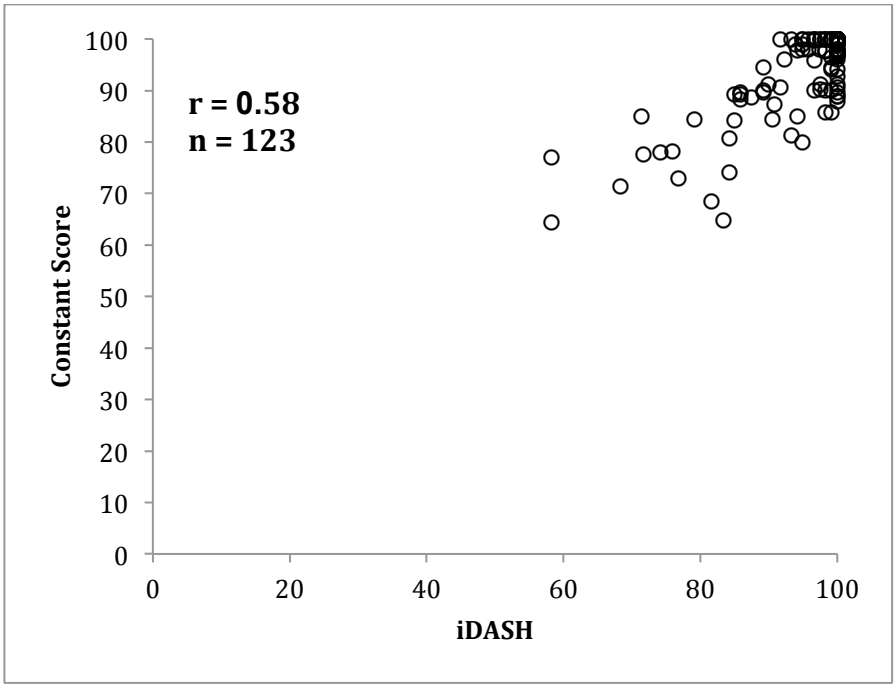


Fig. 6.
Scatterplots of inverted Disabilities of the Arm, Shoulder and Hand (iDASH) and Constant-Murley score (CS) at (A) six weeks follow-up and (B) one year follow-up. r, Spearmans Rank correlations coefficient. n, number of subjects. Reprinted from Acta Orthopaedica under the Creative Commons Non-Commercial License.

Mean bias

At six weeks follow-up the Bland Altman plot (Fig. 7) showed a mean bias towards iDASH of 2.21 (95% CI 0.22 to 4.20).

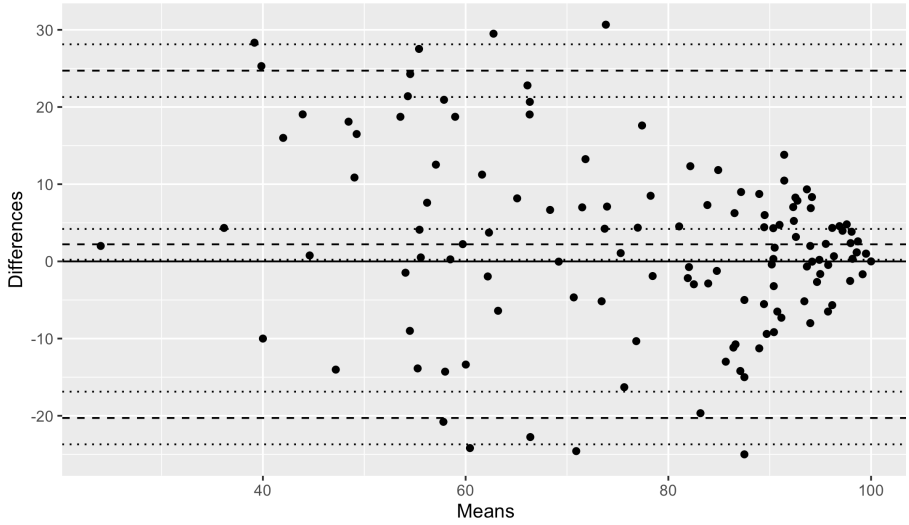


Fig. 7
Bland-Altman plot of the means of inverted Disabilities of the Arm, Shoulder and Hand (iDASH) and Constant-Murley score (CS) versus the differences between iDASH and CS. Top dashed line indicates upper limits of agreement, while lower dashed line indicates lower limits of agreement. Middle dashed line indicates mean bias. Dotted lines show 95 per cent confidence intervals around agreements and mean bias. Reprinted from Acta Orthopaedica under the Creative Commons Non-Commercial License.

6.4 Study III

The cohort for study III consisted of 63 non-operatively treated patients available at six months follow-up and one patient in the operative treatment group who declined surgery after randomization.
We saw a deviation in mean VAS score over time between the two groups (Fig 8.).
This deviation in VAS score was confirmed by our linear mixed effects analysis. After visual inspection of our linear mixed effects model we defined VAS_{ratio} as pain score from week four divided by pain score from week two.

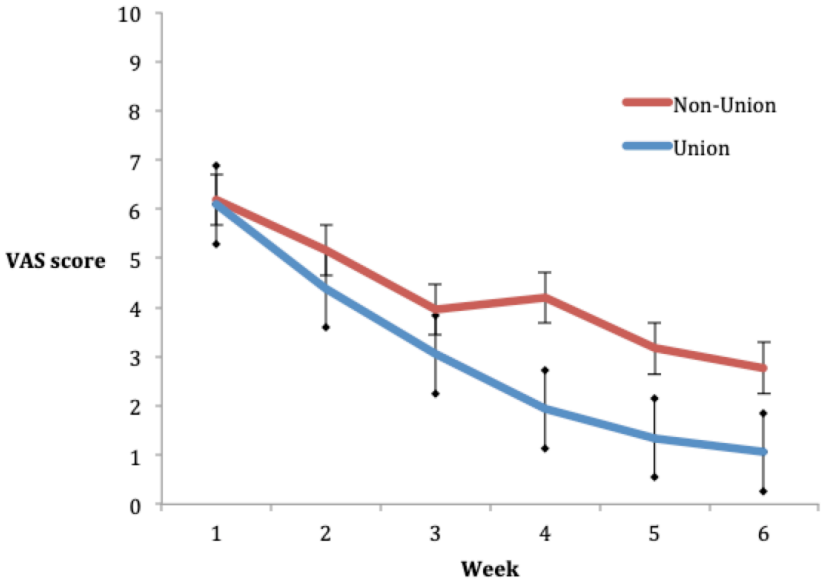


Fig 8. Mean patient reported pain on a visual analogue scale the first six weeks following fracture. Error bars indicate standard error.

Predictors

Pain score at week four (odds 1.84 per 1 point, 95% confidence intervals (CI) 1.08 to 3.4) and VAS_{ratio} (odds 1.06 per 0.01 point 95% CI 1.02 – 1.11) were identified as independent predictors via logistic regression

VAS_{ratio} cohort analysis

After treating VAS_{ratio} as an exposure to a risk factor we used different VAS_{ratio} cut-off points to analyse the cohort in various risk scenarios (Table 4).

A

Cut-off 0.20		
	Union (n)	**Symptomatic non-union (n)**
Exposed	41	11
Control	12	0

AR = 21.2 % (95% CI 11.1 – 34.7)

RR = ∞ (No non-unions in control group)

B

Cut-off 0.60		
	Union (n)	**Symptomatic non-union (n)**
Exposed	13	10
Control	40	1

AR = 43.5 % (95% CI 23.2 –63.7)

RR = 17.8 (95% CI 2.43 - 130.44)

C

Cut-off 1.00		
	Union (n)	**Symptomatic non-union (n)**
Exposed	2	3
Control	51	8

AR = 60 % (95% CI 14.7 – 95.0)
RR = 4.4 (95% CI 1.7 - 11.6)

Table 4. Analysis of cohort at various VAS_{ratio} cut-off points. Exposed group consist of patients above VAS_{ratio} cut-off point. A = VAS_{ratio} cut off at 0.20, B = VAS_{ratio} cut off at 0.6, C = VAS_{ratio} cut off at 1.00. AR and RR = Absolute Risk and Relative Risk of symptomatic non-union in exposed group. (CI = Confidence Interval). Adapted from study III

ROC curve

ROC curve analysis showed that VAS_{ratio} (AUC 0.84 95% CI 0.72 to 0.96) has acceptable discrimination[96](Fig. 9).

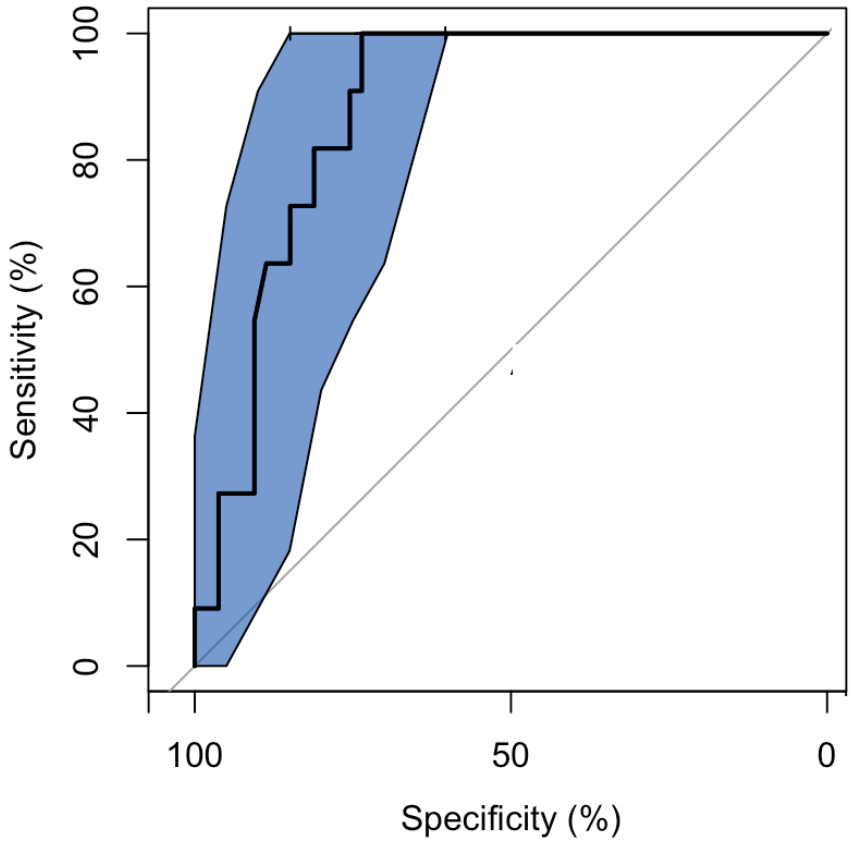


Fig 9. Receiver operating characteristics curve using VAS_{ratio} as a predictor for symptomatic non-union. AUC = 0.84 (95% CI 0.72 to 0.96). Blue shade indicates confidence interval. Adapted from study III

7. Discussion

7.1 Main findings and comparison with the literature

Study I

In study I we found that operative treatment gives early improvements in functional outcome, but this difference between operative and non-operative treatment is not maintained and after six months there is no difference between the two groups. We cannot reject the null hypothesis for study I. Only one randomized trial[16] has shown a 10 point relevant difference in functional outcome scores after one year follow-up. All other randomized trials have shown less than 10 points difference[10,18,19] or no difference[17,20,21] at end-analysis, which is similar to our findings. It is important to notice that some trials[10,18,21] include untreated non-unions in end-analysis, and the exclusion of untreated non-unions from end-analysis improves functional outcomes for non-operative treatment[18]. In this study both treated and untreated non-unions were included according to the intention to treat principle, to reflect a true clinical setup. Furthermore we found that operative treatment of midshaft clavicular fractures reduces the risk of non-union from seventeen to three percent. This risk reduction benefit of operative treatment has been shown several times previously[2,22]. The NNT to avoid one non-union was 7, which is similar to the findings in Woltz' metaanalysis of randomized controlled trials[22]. The main complication following operative treatment was symptomatic hardware, which resulted in reoperation for twenty-five percent of the patients. In studies that systematically reported the need

for plate removal[10,18–21], the removal rates range from 3 percent to 17 percent. In a metaanalysis of recent randomized trials[22] ninety-five per cent of secondary surgical procedures in the operative treatment group was due to symptomatic hardware. Serious adverse events such as implant failure or infection account for sixteen and eleven per cent respectively.
As previolusy decribed in study considerations it is possible that our high rate of plate removals in study I is study induced due to routinely presenting patients with the option of plate removal after six months.

Study II

In study II we demonstrated good convergent validity between DASH and CS. The null hypothesis is rejected and the alternative hypothesis is accepted. The correlation between DASH and CS score was found to be moderate to high. Correlation decreased with increasing follow-up, possibly due to the increasing ceiling effect and decreasing number of subjects. In a wide range of studies including a study on clavicular fractures[40–43] good correlation between DASH and CS has been found, which is consistent with our findings, but simply demonstration correlation between two methods of measurement is not enough to establish convergent validity[97]. A Bland-Altman plot was constructed to further investigate the agreement between DASH and CS. A small bias between DASH and CS of 2.21 points was found in the Bland-Altman plot. To our knowledge this is the first study to construct a Bland-Altman plot of DASH and CS in patients with clavicular fractures. Support for our finding of a small mean bias in the Bland-Altman plot could be indirectly drawn from Woltz' metaanalysis[22], where a similar mean difference of DASH and CS is found.

The convergent validity between DASH and CS allows for the sole use of either score in future studies. Abandoning CS means abandoning a score that arbitrary combines subjective and objective measurement with no reasoning for the selection of items or weight of each item. This lack of underlying logic surrounding the CS is in stark contrast to the DASH questionnaire, which was developed with a systematic approach and a defined purpose[15]. Furthermore the objective part of CS creates a logistic and economic burden compared to DASH, where no trained personal or ambulatory visits are necessary in order to obtain the score. We suggest that only DASH is used in future studies of midshaft clavicular fracures.

Study III

In study III we found that minimal pain reduction from week two to week four is associated with a high risk of symptomatic non-union. The null hypothesis is rejected and the alternative hypothesis is accepted. The absolute risk of non-union increased with increasing VAS_{ratio}. VAS_{ratio} was found to be an excellent discriminator and a cut-off of 0.58 was the optimal value in a model predicting the risk of symptomatic non-union. Compared to the predictive value of DASH score at 6 weeks following fracture[56] with a AUC of 0.70 (95% CI 0.53 to 0.89), the discrimination ability of VASratio (AUC 0.84 (95% CI 0.72 to 0.96) is superior. We did not find DASH score at 6 weeks to be associated with nonunion in our study. Our findings of an association between pain and non-union along with the previous findings of Nowak[54], Clement[53,56] and Nicholson[57] suggests that proxy variables for healing exists as theorized in Fig 2. This allows for the possible development of prediction models without the need of baseline characteristics.

7.2 Limitations and other considerations.

Non union

As described previously the definition of non-union varies across the literature. In study I the rate of non-union was 17 percent. The rate of non-union in randomized trials ranges from 4 percent[16] to 24 percent[17]. Due to the poor definition of non-union and variance in the defining time limit, the rate of non-union across the literature is difficult to compare. Comparing symptomatic non-union rates is even more problematic, as none of the recent randomised trials defines the term "symptomatic".

Malunion

In study I we did not define malunion as a complication. The word malunion derives from the Latin word "malus" meaning "bad, evil, injurious, destructive, improper, wrong" or more figuratively "ill-looking, deformed, defective"[98]. By its etymological origin a malunion is defined as a fracture healed in a deformity which compromises normal function. A possible consequence of this definition could be that the combination of a clavicular fracture healed in non-anatomic position and the presence of any complications would be classified as a malunion, as the definition of a deformity "which compromises normal function" is difficult. This could potentially lead to a malunion diagnosis for every complication following nonoperative treatment of displaced midshaft clavicular fractures. As described previously "a fracture healed with a deformity" and malunion are used synonymous in some of the literature[33]. Unfortunately the interchangeability of "a fracture healed with a deformity" and malunion, gives rise to the term "symptomatic

malunion" to describe a deformed healed fracture combined with symptoms attributed to the deformity. This term "symptomatic malunion" is an oxymoron based on the etymological origin of malunion, where the union already is "evil". Since complications following non-operatively treated midshaft clavicular fractures can range from specific neurological and vascular complications[34] to the more broad complications such as dysfunction and pain[13,33], the term "symptomatic malunion" becomes nothing more than a poorly defined umbrella term. More relevant prefixes could be "radiological" or "clinical" when describing the malunion, but solid definitions of these terms does not exist.

To avoid a poorly defined term we seeked to examine each complication individually and then classify the complication as neurological, vascular, infectious or other. Allthough the assocation was not shown in a large systematic review[35], some studies reports association between shortening and malunion. It is possible that fracture shorting in these studies is a surrogate marker of tissue damage, as theoretically more initial traumatic force is required in fracutures with a high amount of shortening and displacement compared to undisplaced fractures. The pain and discomfort (a "poor" outcome) attributed to malunion could be secondary to the initial damage of the surrounding tissue when the fracture occurs. It is however uncertain if operative treatment reduces the rate of patients with a "poor" outcome, if the outcome is dependant on the level of tissue damage. To truely investigate the clinical relevance of malunion after nonoperative treatment prospective trials with clear definitions are needed.

Drop out and sample size calculation

A risk of type 2 error arises in study I, as only 60 patients were available for end point analysis in the non-operative treatment arm. The sample size calculation assumed a standard deviation in DASH of 20 points. Randomized controlled trials conducted after the initial sample size calculation all have a lower standard deviation, where the highest deviation is 13.5 points[17].
Using this standard deviation a new sample size for each group is calculated as:

$n_a = ((Z_a + Z_{1-b})^2 \text{ x } 2 \times \sigma^2)/d^2$

$n_a = ((1.96 + 0.84)^2 \text{ 2 x } 13.5^2))/10^2$

$n_a = (7.84 \text{ x } 2 \text{ x } 400)/100 = 28.5$

As a sample size calculation based on a more realistic standard deviation only requires 29 patients in each group, we estimate the risk of type 2 error due to lack of power to be low.

Limits of agreement

In study II the Bland-Altman plot shows wide limits of agreement ranging from -20.3 to 24.7 points. This is without consequence as the aim of the study was to investigate the difference between DASH and CS on a multi subject scale and not on an individual level.

Predictors of non-union.

We found no association between non-union and age, gender, fracture comminution or shortening. This could possibly be due to our low sample size and lack of power to detect an association. Alternatively a strong association between non-union and age, gender, fracture comminution or shortening does not exist. Evidence for these associations has been previously shown by Jørgensen[31] to be limited. Interestingly Clement[56] also examined pain as possible predictor, where patients were asked to grade their pain at 6 weeks as "none, mild, moderate or severe". Although 16 of 79 patients in the union group indicated no pain after six weeks, compared to only one of 17 in the non-union group, no association between pain and non-union was found. This lack of association could be due to the measurement of pain on a categorical scale at a single time point. Our study did not have the power to develop a prediction model. However the association between non-union and pain could have been further investigated given an external dataset. Unfortunately e-mail contact to the authors of the recent published randomized trials did not provide such a dataset. The predictive value of VAS_{ratio} remains to be proven before widespread clinical use.

Loss to follow-up and study III

The outcome in study III is non-union. We do not know the non-union rates for patients lost to follow-up. It is entirely possible that patients with early dropout abandoned the study due to pain issues in order to seek treatment elsewhere. As we have shown that early minimal pain reduction is associated with a high risk of non-union it is possible that some potential non-unions are missing from the study along with their pain profile. This is however not a severe limitation, as these hypothetical patients would only further strengthen the association between non-union and pain had they continued in the study.

8. Conclusion

Operative treatment with precontoured plates and locking screws of displaced midshaft clavicular fractures gives higher union rates compared with non-operative treatment. After six months there is no difference in functional outcome score between the two groups. Osteosynthesis almost eliminates the risk of non-union, but routinely operating all fractures is not recommended due to the risk of complications following operative treatment, including the high risk of exposing many patients to unneccesary surgery. It may be possible to reduce the overall group risk of non-union by offering operative treatment to patients at high risk of developing a non-union. Minimal pain reduction in the early weeks after fracture is associated with a high risk of developing a symptomatic non-union, but this association needs to be externally validated, before a treatment algorithm is put to clinical use. In future studies DASH could be used as the sole functional outcome, as there is good convergent validity between DASH and CS.

9. Treat-all, treat-none or treat-some? Perspectives and suggestions for future research.

Research questions asked in randomized trials often yields a strict binary response (treatment: yes/no) and the results from these trial are often (mis)used to adapt a "treat-all" or "treat-none" approach.

The current evidence on the treatment of midshaft clavicular fractures points towards a "treat-none" approach, as the only benefit of treatment is the reduced risk of non-union, and the NNT to avoid one non-union is deemed to high in contrast to the risk of complications associated with surgery.

A different approach could be "treat-some", where only patients at high risk of developing a non-union would be offered surgery. Study III suggests that minimal pain reduction in the early weeks following fracture could be a key component in the development of new treatment algorithm. The end goal of individualized treatment is the reduction of the risk of non-union along with a reduced risk of surgical complications for the whole group.

The treat-some approach could also contain patients, who opt for primary operative treatment. The group includes high demand patient such as athletes (overhead sport or cycling), or patients not willing to accept even a low risk of non-union.

In study III we only show an association between pain and non-union risk, and conclude that these findings should be externally validated before clinical implementation.

This validation before clinical implementation poses a challenge, as true external validation of a predictive model requires a dataset of minimum 100 events[94]. As discussed in the study II paper a dataset of this size would take 18 years years to collect using the original study setup.

A more pragmatic approach would be a new study where the "treat-some" algorithm (with an arbitrary VAS_{ratio} cut-off point) is compared with the "treat-none" approach. In this new study functional results

could be obtained with DASH score alone, as we in study II have shown no need for the simultaneous use of DASH and CS in future studies.

Should the “treat-some” algorithm prove to be superior, a successful nationwide clinical implementation could be proved in register studies following the years after implementation, where one would a expect to see a reduction in the nationwide rate of non-union along with a low rate of primary surgery.

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